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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,437	11/16/2001	David Botstein	P2730P1C49	2360

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,437	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124,129-131 and 135-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124,129-131 and 135-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Inventorship

In view of the papers filed 2/3/05, the inventorship in this nonprovisional application has been changed by the deletion of A. Ashkenzai, K. P. Baker, L. Desnoyers, D.L. Eaton, N. Ferrara, S. Fong, H. Gerber, J. C. Grimaldi, I. J. Kljazin, M. A. Napier, J. Pan, N. Paoni, D. Tumas, Z. Zhang, M. E. Gerritsen, T.A., Stewart. C. K. Watanabe and P. M .Williams.

Response to Amendment

The Declaration of Goddard et al. under 37 CFR 1.132 filed 02 August 2005, is insufficient to overcome the rejection of claims 124, 129-131 and 135-138 based upon 35 USC § 101 and 112, first paragraph, as set forth in the last Office action because: it does not establish that the amplification of the encoding nucleic acid in tumors is sufficient to establish utility or enablement for the nucleic acid or encoded protein as discussed below.

Claim Rejections - 35 USC § 101 and 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 124, 129-131 and 135-138 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons previously set forth and as recast here.

The instant claims are drawn to a nucleic acid comprising SEQ ID NO:32 or the full-length coding sequence of the cDNA of ATCC 209790. The nucleic acid was found to be

amplified in squamous cell-type lung carcinomas, with 5/11 SqCCa showing a $\Delta Ct > 1.0$ and 2/17 colon tumor samples with $\Delta Ct > 1.0$. However, the significance of the ΔCt was based on the use of normal controls of genomic DNA from human blood (pages 547-548) and did not take into account controls for aneuploidy of the tumor tissue used. At page 545, Ct is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification indicates that Ct is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO290 shows a positive correlation with lung SqCCa or other cancer, much less that the levels of PRO290 would be diagnostic of such. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Thus, the data do not support the implicit assertion that PRO290 can be used as a cancer diagnostic.

While the nucleic acid showed slight amplification in tumor cells, particularly lung squamous cell carcinomas, compared to normal tissue, this does not support a diagnostic use of the nucleic acid for detection of cancerous tissue. Hittelman (Ann. NY Acad. Sci., 952:1, 2001) showed that chromosomal polysomy occurred with a much greater likelihood in cancerous compared to adjacent normal epithelium (p. 6, third paragraph). That means an increased copy number for PRO290 in lung tumors tested was less likely due to an increase unique to PRO290 DNA, but rather due to a more general phenomenon of polysomy of the DNA in epithelial cancers. Additionally, it was also found that, "[T]he presence or absence of squamous metaplasia at biopsy site does not necessarily correlate with the degree of underlying genomic instability," (p. 8, second paragraph). Further, in individuals who had stopped smoking, chromosomal instability was still evident despite the decrease risk of lung cancer, drawing the conclusion that "individuals are differentially sensitive to carcinogenic insult," (p. 8, end of third paragraph). Because of the above considerations, significant further research would have been

required of the skilled artisan to determine whether PRO290 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial or specific.

Further, the polynucleotide cannot derive a utility from the encoded polypeptide because there is no reasonable expectation that there is alteration of polypeptide sequence or amount in colon or lung tumors *versus* normal colon or lung tissue. Also, there is no known specific and substantial function of the polypeptide. In this instance, the encoded polypeptide cannot bring utility to the encoding polynucleotide or *vice versa*. It is not known what the protein does or if the level of the protein of SEQ ID NO:33 in colon or lung tumors corresponds to mRNA transcript level or gene levels. There are several valid reasons to support the unpredictability of correspondence between nucleic acid and protein expression, including: differences in mRNA lifetime, protein translation efficiencies, protein stabilities and amount of protein post-translational modification. For example, Haynes et al. (Electrophoresis 19:1862-1 87 1 , 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1 863, second paragraph, and Figure 1). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Lian et al. (Blood 1 :513-524, August 2001) examined mRNA *versus* protein levels in differentiating myeloid cells (MPRO cells), concluding (p. 514, end of 2nd full paragraph) that, "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels...." In the discussion, Lian et al. note (p. 522, first sentence of each of last two paragraphs), "The discrepancies between mRNA and protein levels in MPRO cells appear to be substantially larger than those observed for yeast. Possible causes for the discrepancies include translational regulation, differential expression of certain mRNAs at various stages of cell growth in vitro, post-translational protein modification that varies with the state of maturation of the cells, and selective degradation or excretion of proteins in vivo.... The initial studies of protein expression presented here provide a cautionary note for efforts to interpret cell composition and function in relation to mRNA levels." In a

separate comparison by Fessler et al. (J. Biol. Chem. 277(35): 31291-302, Aug. 2002) examining lipopoysaccharide-activated neurophils (col. 2, beginning of last paragraph on p. 31300) they state, "Parallel use of DNA microarrays and proteomics affords a powerful strategy for comparison of corresponding mRNA transcripts and proteins, thereby affording new insights into mechanisms by which the cell regulates its signaling response to the external environment. Of interest, a poor correlation was also found between corresponding transcripts and proteins (Table VIII), as reported in other systems." They warn (first sentence p. 31296), "Nevertheless, the reliance upon DNA microarrays alone affords insight only into the transcriptional response without corroboration at the protein levels." In terms of gene amplification and protein expression, Pennica et al. (1998, PNAS USA 95:14717-14722), show a lack of correlation between gene amplification and overexpression in two out of three WISP genes. Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) state that polypeptide expression correlated with mRNA levels, but not gene amplification for the abl gene.

The claims are drawn to a polynucleotide. The specification asserts a number of utilities for both the polypeptide and encoding polynucleotide, however, these utilities are not specific and substantial or well established. For example, in Example 144, it is asserted that the polypeptide may be used as an antigen to make antibodies. Because neither the physiological nor the clinical significance of the polypeptide is disclosed, and because the prior art does not support a very close structural relationship to a disclosed well described family of known proteins disclosed in the specification by both structure and function, the polypeptide and encoding polynucleotide do not have utility as required by 35 USC 101. If the polypeptide antigen does not have utility, then the antibody which binds it (or method of making the antibody) does not have a specific and substantial utility.

Another example of utility is in drug screening and rational drug design (Examples 146 and 147, respectively). The methods involve screening for "agents which can affect a PRO polypeptide-associated disease or disorder" (p. 521, line 32). No disease or disorder is known to be associated with the encoding polynucleotide or encoded polypeptide. In order to discern a utility for the claimed polynucleotide through drug screening in the absence of guidance about which type of disease or disorder the encoding polynucleotide or encoded polypeptide causes or how its involvement could lead to treatment, screening for drugs by using the polynucleotide or

encoded polypeptide would still require further and undue experimentation to determine the significance of an agent that somehow influenced the polynucleotide's or polypeptide's function.

It is asserted that the encoding PRO polynucleotide can be used in tissue typing or chromosome marking. This asserted utility is not specific or substantial. All genes have a chromosomal location and, with the exception of a few housekeeping genes, have a tissue specific pattern of expression. Thus virtually any polynucleotide can be used in chromosomal marking or tissue typing. Therefore, the asserted utility is not specific to PRO290. The encoded polypeptide likewise cannot have a specific utility based on tissue typing.

Lastly, in Figure 22 of the instant application, it is indicated that the encoded polypeptide has an N-glycosylation site and N-myristoylation sites, cAMP and cGMP-dependent protein kinase phosphorylation sites and tyrosine kinase phosphorylation sites; however, none of these sites alone or in combination provides sufficient information for the skilled artisan to readily identify a specific and substantial use for the polypeptide or encoding nucleic acid.

For these reasons, there is no substantial and specific utility for the claimed polynucleotide.

Claims 124, 129-131 and 135-138 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

It would require significant further experimentation to be able to use the claimed polynucleotide because no particular function or specifically associated disease has been determined for the polynucleotide of SEQ ID NO:32, and there is no disclosed definite function supported by the prior art. No function can be reasonably assigned based on its homology to another polynucleotide(s). Using the claimed polynucleotide would require undue experimentation.

Applicants arguments are directed to both the rejection under 35 USC 101 and 112, first paragraph, enablement, and will be addressed here together.

At pages 4-5 of Applicants' response, it is argued that the data in Example 170 (starting at p. 539 of the specification) describes results of a gene amplification assay. Applicants characterize the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Applicants assert that gene amplification is an essential mechanism for oncogene activation. Applicants review how the assay was performed, and reports that the gene encoding PRO290 was significantly amplified (2.297-fold to 4.2-fold) in 5/19 lung tumors. This has been fully considered but is not found to be persuasive. First, it is important to note that the gene encoding PRO290 was not found to be amplified in 14 out of nineteen lung tumors (6/11 SqCCa-type tumors) and 15/17 colon tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 547). The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung and colon, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy (see Sen, Hittelman). Given these details, one skilled in the art would not conclude that the gene encoding PRO290 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results.

On page 5 of the Response, Applicants refer to the declaration of Dr. Goddard, submitted under 37 C.F.R. § 1.132 on 02 August 2005, as a copied from a different case (09/903,925). Applicants quote from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Applicants conclude that one skilled in the art would consider the 2.297-fold to 4.2-fold amplification of the gene encoding PRO290 in 5 lung tumors is significant and credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993 In the instant situation, the nature of the fact sought to be established is

whether or not a 2.297- to 4.2-fold amplification of the gene encoding PRO290 in five lung tumors is significant and credible. Credibility has never been questioned. However, the significance can be questioned since 14 out of nineteen lung tumor (6/11 SqCCa-type tumors) and 15/17 colon tumor samples did not show an amplification of the gene encoding PRO290, and the control used was not a matched non-tumor lung or colon sample, respectively, but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). Pennica et al. and Konopka et al. speak to the strength of the opposing evidence, as does Hittelman and Sen who indicate that gene amplification occurs in non-cancerous tissue because of aneuploidy. The expert has interest in the outcome of the case since Dr. Goddard is listed as an inventor and is employed by the assignee. Finally, the expert refers to three publications as factual support for the conclusions in the declaration. However, none of Livak et al., Heid et al., nor Pennica et al. appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors. The Goddard declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO290 gene has *not* been associated with tumor formation, the development of cancer, the progression of cancer, the prediction of cancer, or the recovery from cancer during treatment. The specification merely demonstrates that the PRO290 genomic DNA was amplified in some cancers, to a minor degree (about 2.5 fold), relative to normal blood DNA. No mutation or translocation of PRO290 has been associated with any type of cancer versus normal tissue. It is not known whether PRO290 is amplified in corresponding normal tissues, and what the relative levels of amplification are. In the absence of any of the above information, all that the specification does is indicate that the DNA encoding PRO290 may be amplified in a variety of samples and invites the artisan to determine the significance of this increase. The specification presents a mere invitation to experiment. Based on consideration of the evidence as a whole, the rejection is proper.

In the middle of page 5 of the Response, Applicants argue that it is well known that gene amplification occurs in most solid tumors, including lung carcinomas, and is generally associated with poor prognosis. Applicants concludes that the PRO290 gene becomes an important diagnostic marker to identify malignant lung or colon carcinomas, even when the lung or colon malignancy associated with PRO290 molecule is a rare occurrence. This has been fully

considered but is not found to be persuasive. As discussed in the rejection above, gene amplification is common in non-cancerous colon and lung epithelium based on the damage the epithelium suffers from exposure to the environment. See Sen and Hittelman et al. There is no control for non-cancerous lung tissue, and thus the relevance of the data in the specification is not clear. Furthermore, there is no disclosure of a correlation of amplification with tumor formation, progression, severity, etc., all of which speak to prognosis. In the instant case, the asserted utility that PRO290 nucleic acids are useful as diagnostic markers for cancer is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO290 nucleic acid to be useful as a cancer diagnostic agent, there must be a detectable change in the amount or form of PRO290 nucleic acid between cancerous and healthy tissue. In the instant case, the evidence of record indicates that the initial gene amplification assay only showed a positive result for five out of nineteen lung cancer samples and two out of seventeen colon cancer samples, and did not take into account aneuploidy in cancerous and non-cancerous lung or colon tissue (lack of matched tissue sample control, lack of aneuploidy control). In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the claimed nucleic acids, and would have had to experiment further to reasonably confirm whether or not PRO290 nucleic acids can be used as a cancer diagnostic agent.

Applicants argue (pages 5-6-) that Sen teaches that aneuploid tissues are cancerous of pre-cancerous. This argument has been fully considered but is not deemed persuasive. Applicants statement is erroneous. Sen includes no teaching that all aneuploid tissues are cancerous or pre-cancerous. Rather, Sen states that cancerous tissues are known to be aneuploid. It is also true that pre-cancerous tissues *may* be aneuploid. The converse is *not* true. Aneuploidy is also a feature of damaged tissue, and is commonly found in colon and lung tissues, which are subject to environmental damage. It does not invariably lead to cancer.

Applicants argue (page 6) that Hittelman studied premalignant lesions and suggested that epithelial tumors develop through a multistep process driven by genetic instability. Applicants state that Hittelman showed that a subset of the same molecular changes found in tumor were also found in premalignant lesions, suggesting that the premalignant lesions might represent precursor lesions for associated tumors. Applicants submit that, contrary to the rejection, the

Hittelman reference supports Applicants' position that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk. Applicants point to Hittelman's statement that it is important to identify individuals at increased risk for developing cancer who might benefit from different types of intervention. Applicants urge that, even if the observed PRO290 amplification were due to chromosomal aneuploidy, identifying genetic markers with this aneuploidy is a very important and useful step in identifying individuals at increased risk of cancer. Applicants conclude that Hittelman supports at least one utility of the claimed PRO290 nucleic acids. Applicants urge that the skilled artisan would know that early detection of lung cancer provides information about risk assessment, prognosis, and therapy. This has been fully considered but is not found to be persuasive. The instant specification does not assert that PRO290 can be used as a precancer marker or as a cancer risk determining agent. The specification does not disclose whether PRO290 gene is amplified only in lung tumor, or also in precancerous lung, or also in healthy lung. Given that proper controls were not done (i.e., comparing gene amplification levels between cancerous and non-cancerous matched tissues), and that PRO290 was positive in only 5 out of 19 lung and 2 out of 17 colon tumor samples, further research would reasonably be required of the skilled artisan to confirm the utilities asserted in the specification and the Response. Such a requirement for further research indicates that the asserted utilities are not substantial. Without knowing Ct levels for normal matched tissue, one cannot conclude that the indication of amplification of PRO290 is a marker for cancer.

Applicants argue on p. 7 that the Jeanfaivre et al. references addresses aneupolidy with respect to cancer survival. The Examiner agrees. The reference of Jeanfaivre does not appear to bear on the issue at hand.

On page 7 of the Response, Applicants argue that beta-actin and GAPDH were used as internal controls. Applicants also point to the use of a negative control of pooled DNA isolated from the cells of ten normal healthy individuals. Applicants assert that the protocols and controls are art accepted. Applicants urge that the same protocols and controls have been used to identify several other tumor markers for various cancers, and that the art and the USPTO have accepted the same protocol and controls as credible. Applicants indicate that several patent applications have been allowed based on the same protocol and controls. Applicants urge that the Examiner is applying a heightened utility standard in this instance, which is legally incorrect. This has

been fully considered but is not found to be persuasive. The beta-actin and GAPDH controls do not speak to the issue of whether PRO290 is also amplified in non-cancerous lung tissue. The pooled DNA from ten normal healthy individuals was isolated from blood cells, not lung or colon tissue, and thus does not constitute a matched tissue negative control. There is no evidence to support Applicants' assertion that the art accepts these controls. Finally, each patent application is examined on its own merits. The other patent applications to which Applicants refer may have reported amplification in a higher percentage of tissues tested, or may have disclosed different experimental details, or had other evidence submitted during prosecution.

On page 8 of the Response, Applicants argue that the specification shows that the gene encoding PRO290 was significantly amplified 2.297-fold to 4.2-fold in five lung tumors. Applicants argue that the fact that 5 out of 19 lung tumor samples and 2 out of 17 colon tumor samples tested positive in the gene amplification assay does not make the gene amplification data less significant or spurious. Applicants reason that some tumor markers are useful for identifying rare malignancies. Applicants argue that such rare tumor markers have great value in tumor diagnosis, prognosis, and classification of tumors. Applicants conclude that it is not relevant to utility whether the PRO290 gene was amplified in five lung tumors or most lung tumors sampled. This has been fully considered but is not found to be persuasive. The gene amplification data presented in the specification were problematic. The control DNA was from blood rather than from a matched tissue sample (i.e., healthy lung), while the literature shows that matched tissue samples are the standard (Pennica et al., Konopka et al.). Also, the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung (Sen, Hittelman). Therefore, it is not clear that the reported amplification is significant. Furthermore, the lung tumor samples in which PRO290 was reported as being amplified were not of the same type. For example, PRO290 tested positive in LT11 and LT13 (p. 161). These are described in the specification as corresponding to stage IIA squamous cell carcinoma and stage IB adenosquamous cell carcinoma. Other lung tumor samples of the same types did not test positive for PRO290 gene amplification. Therefore, the relevancy of Applicants' comments regarding rare malignancies is not clear. If PRO290 were amplified in all stage IIA squamous cell carcinomas, for example, but no other lung carcinomas, such would appear to indicate that PRO290 was a significant rare malignancy marker for stage IIA squamous cell carcinoma.

However, no such trend was disclosed. The specification does not disclose any special feature or prognosis of lung or colon tumors that amplify the PRO290 gene compared to lung or colon tumors that do not amplify the PRO290 gene. It is left to the skilled artisan to determine the significance (if any) of such a difference. Such constitutes the type of further research required to bestow a substantial utility on the claimed invention.

Applicants conclude that the rejection is not based on a *prima facie* case of lack of utility. Applicants urge that the rejection should be withdrawn for lack of evidence. This has been fully considered but is not found to be persuasive. The gene amplification assay disclosed that PRO290 was amplified in five out of nineteen lung tumor samples and two out of seventeen colon tumor samples compared to normal blood DNA. Even *if* the data demonstrated a slight increase in copy number of PRO290 genomic DNA in primary tumors, such would not be indicative of a use of the claimed nucleic acids as diagnostic agents. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean that the nucleic acid is a cancer marker, but can merely be an indication that the cancer tissue is aneuploid. Furthermore, the literature reports that and colon and lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy *before* the cells turn cancerous. See Hittelman (2001, Ann. NY Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay in the specification does not provide a direct comparison between the lung tumor samples and normal lung epithelium. Rather, the assay discloses amplification of PRO290 genomic DNA in lung tumors compared to "normal human DNA" (apparently from blood samples), and thus a skilled artisan would not conclude that PRO290 genomic DNA is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO290 genomic DNA is a diagnostic probe for lung cancer unless it is clear that PRO290 genomic DNA is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium. Also, while it might be argued in hindsight that PRO290 would still be a marker at least for precancerous, or damaged, lung epithelium, such is not suggested by the specification as originally filed and is not well-

established in the prior art. Since the skilled artisan would have to conduct further research to reasonably confirm that PRO290 DNA can be used as a cancer diagnostic agent, the asserted utility is not in currently available form, and is not substantial.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

October 14, 2005

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600